Journal of the Neurological Sciences 284 (2009) 140–143

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Diabetes mellitus and drug-induced parkinsonism: A case–control study

Hyeo-Il Ma [a], Jin-Hyuck Kim [b], Min-Kyung Chu [a], Mi-Sun Oh [a], Kyung-Ho Yu [a], Jooyong Kim [a], Woong Hahm [b], Yun Joong Kim [a,c,*], Byung-Chul Lee [a]

[a] Department of Neurology, Hallym University College of Medicine, Hallym University Sacred Heart Hospital, Anyang, Republic of Korea
[b] Department of Neurology, Keyo Medical Foundation, Keyo Geriatric Hospital, Anyang, Republic of Korea
[c] ILSONG Institute of Life Science, Hallym University, Anyang, Republic of Korea

ARTICLE INFO

Article history:
Received 1 November 2008
Received in revised form 29 April 2009
Accepted 7 May 2009
Available online 20 May 2009

Keywords:
Drug-induced parkinsonism
Diabetes mellitus
Risk factor
Case–control study

ABSTRACT

To investigate if diabetes is more common in drug-induced parkinsonism patients. We performed a hospital-based retrospective case–control study on 44 drug-induced parkinsonism (DIP) patients, 177 Parkinson disease patients, and 176 acute stroke patients matched for age and sex who were seen over the same period at the same hospital. The frequency of diabetes, age-at onset and sex were compared between DIP and IPD or acute stroke. Multivariate analysis showed that patients with diabetes are more frequent in DIP compared with IPD ($p<0.001$, adjusted OR 5.48; 95% CI, 2.52–11.94). The frequency of diabetes in DIP was comparable to that in acute stroke patients ($p=0.16$, adjusted OR 0.62; 95% CI, 0.32–1.21). These data suggest that diabetes may be a risk factor for DIP. Drugs with dopamine receptor blocking potency should be avoided in elderly with diabetes.

1. Introduction

Drug-induced parkinsonism (DIP) which constitutes 15–60% of all parkinsonism is second most common cause of parkinsonism [1–4]. Currently, common causative drugs have changed from classic neuroleptics to benzamide derivatives (sulpiride, levosulpiride, clebopride and metoclopamide), calcium channel-blocking agents (flunarizine, cinnarizine), and atypical neuroleptics [5–8]. Although DIP is a heterogeneous clinical syndrome where not only blockage of dopamine D2 receptor but also subclinical parkinsonism is a possible cause, older age and female gender were consistently reported as risk factors for DIP [9,10]. Besides, diabetes mellitus (DM), chronic renal failure, past brain insults, or genetically determined differences in drug metabolism were also suggested as a risk factor for DIP [11–16]. The relationship between DIP and DM has not been systematically studied yet, although coexisting tardive dyskinesia and parkinsonism were reported to be associated with diabetes [17]. We carried a retrospective study to investigate the association between DIP and DM by comparing the frequencies of DM among patients with DIP, idiopathic Parkinson disease (IPD), and acute stroke.

2. Subjects and methods

We retrospectively reviewed medical records of patients who visited movement disorders clinic at Hallym Sacred Heart hospital and diagnosed as DIP or IPD from Jan 2003 to Aug 2007. DIP was defined according to the following criteria: 1) the presence of at least two of four cardinal signs (tremor, rigidity, bradykinesia, and impaired postural reflexes); 2) absence of a personal history of extrapyramidal disorders before treatment with an offending drug; 3) onset of symptoms in the course of treatment with an offending drug; 4) reversal of parkinsonian symptoms, although not necessarily completely resolved, after discontinuing offending drugs during follow-up for more than 3 months [7]. IPD was diagnosed according to the United Kingdom Parkinson Disease Society Brain Bank clinical diagnosis criteria [18]. Other secondary causes of parkinsonism including vascular parkinsonism were excluded by neuroimaging studies (CT or MRI) and appropriate laboratory tests. All DIP and IPD were seen and diagnosed by one of two movement disorders specialists (HIM or YJK).

Another disease control of acute stroke where DM is a well-recognized risk factor was used to compare the frequency of DM with DIP. A blinder (MSO) selected 4 controls per case from Hallym Stroke Registry [19] of the same sex and age (±1 year). The diagnosis of acute stroke was based on clinical findings and neuroradiological studies simultaneously reviewed by two experienced neurologists (KHY and BCL). Stroke subtypes of all patients enrolled in Hallym Stroke Registry were based on the modified Trial of Org 10,172 in Acute Stroke Treatment (TOAST) classification using a consensus approach [20]. Stroke control patients were selected from the subtypes of large-

* Corresponding author. Department of Neurology, Hallym University Sacred Heart Hospital, Room 607, ILSONG Building, 1605-4 Gwanyang-dong, Dongan-gu, Anyang, Gyonggi-do 431-060, Republic of Korea. Tel.: +82 31 380 1666; fax: +82 31 388 3427.
E-mail address: yunkim@hallym.ac.kr (Y.J. Kim).

0022-510X/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.jns.2009.05.006

Table 1
Demographic characteristics of patient groups.

	DIP ($n = 44$)	IPD ($n = 177$)	Stroke ($n = 176$)	Odds ratio (95% CI, lower–upper)[§]	
				DIP vs IPD	DIP vs stroke
Sex (M:F)	11:33	67:110	44:132	N/A	N/A
Age-at-onset (years) (mean ± SD)	70.4 ± 6.7	63.3 ± 11.7[*]	70.2 ± 6.6	N/A	N/A
DM (%)	20 (45.5)[**]	21 (11.9)[**]	21 (34.1)[**]	5.48 (2.52–11.94)[†]	0.62 (0.32 –1.21)[‡]

[*] $p<0.001$ compared with DIP.
[**] Values are number of patients with DM.
[†] $p<0.001$.
[‡] $p = 0.16$.
[§] Odds ratio after multivariate adjustment.
NA, not applicable.

artery atherosclerosis (LAA), or small-vessel occlusion (SVO) since diabetes is an established risk factor for these subtypes of stroke. The study protocol was approved by the institutional review board at Hallym University Sacred Heart Hospital.

We investigated presence of DM at the age-at-onset of DIP, IPD or stroke. Assessment of the history of type 2 DM was first based on self-reporting on history taking. History of DM was defined as ever reporting of doctor-diagnosed diabetes regardless of diabetic medication. All patients had undergone blood tests to measure blood sugar level when they first visited our clinic. DM was confirmed by applying the following criteria: one or more classic symptoms and a fasting plasma glucose level >7.8 mmol/l; at least one raised plasma glucose concentration on a fasting plasma glucose level >7.8 mmol/l; or treatment with a hypoglycemic drug (oral anti-diabetic agents or insulin) [21].

Multiple logistic regression analysis was used to compare frequency of DM between the IPD and DIP groups. Chi-square test was used to compare the frequency of DM between DIP and acute stroke patients matched for age and sex. Unpaired *t*-test was used for comparison of age-at-onset, latency of drug exposure, and Hoehn & Yahr stage between DIP with DM and DIP without DM. A p value of <0.05 was regarded as being statistically significant. The statistical analyses were performed using commercially available software (SPSS, version 12.0).

3. Results

During the period indicated above, 44 patients were diagnosed with DIP and 177 patients were diagnosed with IPD. In both groups, female to male ratio was high, however, there was no difference of sex ratio between two groups. The mean age-at-onset of Parkinsonian symptoms was higher in the DIP group than the IPD group (Table 1), which is consistent with previous reports [7,10]. The mean (SD) duration of Parkinsonian symptoms in DIP was 6.3 (7.2)months, ranging from 0.5 to 36 months. Levosulpiride was the most common offending drug ($n = 24$), followed by perphenazine ($n = 7$), flunarizine ($n = 6$), metoclopropamide ($n = 5$), clebopride ($n = 2$), risperidone ($n = 2$), and chloropromazine ($n = 1$). Three patients were taking two offending drugs concomitantly. In levosulpride-induced parkinsonism, male to female ratio was 7:17, and the mean age-at-onset was 71.5 ± 7.5 years. DIP occurred after a mean (SD) exposure of 12.6 (12.3) months to the offending drugs. The most common indication for the use of the offending drugs was gastrointestinal symptoms ($n = 24$). Other indications include anxiety ($n = 6$), dizziness ($n = 4$), headache ($n = 2$), insomnia ($n = 2$), psychosis ($n = 1$) and unknown reasons ($n = 5$). In the 24 DIP cases caused by levosulpiride, the drug was used for gastrointestinal symptoms ($n = 17$), anxiety ($n = 3$) and unknown reasons ($n = 4$).

To explore if DM is more common in DIP, we compared the frequency of DM between DIP and IPD. Patients with DM were significantly more frequent in DIP compared to the IPD group even after multivariate adjustment for age and sex ($p<0.001$, OR 5.48; 95% CI, 2.52–11.94) (Table 1). The mean (SD) duration of DM in DIP group was 14.7 (12.4) years. To control for bias caused by different medications, we repeated the same analysis between a subgroup of DIP caused by levosulpiride, a gastrointestinal motility drug with D2 blocking potency, and IPD. Fourteen (58.3%) out of 24 patients with levosulpiride-induced parkinsonism had DM, which was higher compared with IPD ($p<0.001$, OR 9.08; 95% CI, 3.19–25.78). Because DM is an established risk factor for acute stroke, we compared the frequency of DM in DIP patients with acute stroke patients. Out of 176 acute stroke patients matched for age and sex, 60 (34.1%) patients had diabetes, and there was no difference in the DM frequency between the two groups ($p = 0.16$, OR 0.62; 95% CI, 0.32–1.21). We hypothesized that the presence of DM renders the striatal neurons more susceptible to dopamine receptor antagonists and compared the following variables between the DIP groups with and without DM: the age-at-onset of parkinsonism, disease severity as measured by initial Hoehn & Yahr stage, and latency of an offending drug exposure. There was no difference of the above parameters between the two groups (Table 2). To avoid the effect of different D2 receptor blocking potencies of various drugs, we chose 24 DIP cases caused by levosulpiride and repeated the same analysis. However, there was no difference of the above parameters between levosulpiride-induced parkinsonism with and without DM (data not shown).

4. Discussion

Consistent with previous reports [9,10], known risk factors for DIP such as old age and female gender were more frequent among DIP patients in our data. Intriguingly, female preponderance was observed in both the DIP and IPD groups. Series of DIP patients from another tertiary referral hospital in Korea reported that more than 75% of the patients were female [7,22]. Although many epidemiological studies have reported that IPD is slightly more common in men than in women [23,24], female preponderance was reported in a number of epidemiological studies from Japan and Korea [25,26]. Therefore, the female preponderance observed in our study may be due to ethnic background rather than selection bias.

Table 2
Comparison of clinical characteristics between DIP with diabetes and without diabetes.

	DIP with DM ($n = 20$)	DIP without DM ($n = 24$)	p value
Sex (M:F)	4:16	7:17	0.78
Age-at-onset (years)	68.8 ± 7.8	71.7 ± 5.6	0.15
Latency (months)	11.7 ± 10.5	13.3 ± 14.0	0.71
Initial Hoehn & Yahr stage	2.1 ± 0.5	2.0 ± 0.6	0.28

Studies on medical conditions as a risk factor for DIP are rare. Past brain insults or renal failure have been reported to increase the risk for DIP [11,15]. In a study with schizophrenia patients, coexisting tardive dyskinesia and parkinsonism after neuroleptic treatments was associated with diabetes [17]. We showed that 45.5% of the DIP patients had DM. The prevalence of DM increases with age and reaches its peak in the oldest female group [27]. The proportion of IPD with DM in our data appears larger compared to the two previous case–control studies on DM in IPD [28,29]. This difference may be explained by the difference of mean age of patients or ethnic background. A nationwide survey of Korean men and women above the age of 60 found the crude prevalence of DM to be 15–25% [27], which is close to the frequency of DM in the IPD group in our data. Since it is difficult to estimate the prevalence of DM in age- and sex-matched control population, we used two disease controls for comparison. The frequency of DM was higher in DIP than in IPD in our study, although epidemiological studies on the relationship between diabetes and Parkinson disease or other parkinsonism have been sparse, and results are inconsistent [21,28–32]. In a review by Sandyk, estimates of impaired glucose tolerance in IPD range from 50 to 80% [33]. In a national survey of 24,831 US elderly adults, the investigators found that the prevalence of DM among adults with parkinsonism or IPD was higher compared to the people without those conditions (29.7% vs. 21.5%) [34]. However, case–control studies on the relationship between IPD and DM suggest that diabetes was associated with reduced risk for IPD [28,29]. Two recent prospective studies investigating the effect of DM on the development of IPD reported contradictory results. In two large US cohorts of the Nurses' Health Study (121,046 women) and the Health Professionals Follow-up Study (50,833 men), risk of PD was not associated with self-reported history of diabetes [30]. In contrast, in another cohort of 51,552 Finnish men and women, type 2 diabetes increases risk for PD even after multivariate adjustment including coffee, alcohol consumption, BMI, serum lipids and physical activity [21]. Therefore, our finding that diabetes is more common in DIP than in IPD suggests that diabetes may be a risk factor for DIP. In acute stroke, diabetes is a well-recognized risk factor. In a prospective multi-center cooperative hospital-based nationwide stroke registry study in Korea, the frequency of diabetes in acute stroke patients admitted to hospitals was 28.5% [35]. Given that frequency of diabetes in DIP was comparable to that of acute stroke in our data, diabetes may be a risk factor for DIP like acute stroke. Most of medical conditions associated with drug-induced parkinsonism are simply co-morbidities which an offending drug is prescribed for [10]. That dopamine antagonists are not used in the regular treatment of diabetes suggests that higher frequency of diabetes in DIP is not likely co-morbidity.

Although there are some controversies, preclinical and clinical evidence suggests that chronic hyperglycemia or DM may affect basal ganglia directly or increase susceptibility to a basal ganglia disorder. Tardive dyskinesia caused by chronic neuroleptic treatment is more common in DM patients than in non-DM [17,36]. Non-ketotic hyperglycemia in DM patients sometimes induces chorea with hyperintense lesion in basal ganglia on T1-weighted MR image especially in Asian [37]. In animal studies, chronic hyperglycemia decreased striatal dopaminergic transmission [38]. Based on these evidences, we hypothesized that the DIP patients with diabetes had a shorter latency of drug exposure and more severe clinical phenotype than the DIP patients without DM. However, because of small sample size, wide range of latency, and crudeness of clinical severity scale of Hoehn & Yahr stage, we failed to prove our hypothesis.

Limitations of this study include the following. First of all, this is a retrospective case–control study in which the temporal relationship between diabetes and DIP onset may be unclear. Since this study was conducted in a tertiary referral center, there might have been selection bias. More importantly, the frequency of DM in the DIP group might have been exaggerated because those with DM are more likely to seek medical service, and therefore are more likely to be exposed to the offending drugs. Alternatively, patients with DM who developed gastroparesis might have been given levosulpiride or other anti-emetics with some of these patients subsequently developing DIP. Cigarette smoking which is inversely related with the risk for IPD might have had protective effect on the development of DIP. However, considering that smoking in aged women in our society is really rare and women were more common in DIP population, analyzing the effect of smoking in this study may be biased. Secondly, since our DIP patients are old, and we do not have long term follow-up data of more than 3 months, some preclinical IPD patients unmasked by the offending drugs might have been included in the DIP group. A large prospective study with long term follow-up is needed to solve these problems. Thirdly, although DM could have been induced or exacerbated by the offending drugs in the DIP group as reported previously [39,40], we think that the possibility is low in our series because the mean duration of DM in the DIP group is much longer than the mean latency of exposure to the offending drugs. Finally, we did not confirm the agreement between the self-reported history of DM and the clinical confirmation of ICD-9 codes for DM. We think this might not have influenced results of this study, because there was substantial agreement between self-reported DM and the ICD-9 codes for DM (kappa = 0.76) [28]. Despite these limitations, our result showing an increased DM frequency in DIP has an important implication in clinical practice. Although anti-dopaminergic gastro-intestinal prokinetics are recommended to treat diabetic gastroparesis [41,42], caution should be exerted in the use of these drugs especially on elderly women with DM.

Funding

This work was supported by a grant from Hallym Medical Center (01-2004-23).

Competing Interests

There are no competing interests in all authors.

Acknowledgements

The authors would like to thank Dr. Lee PH and Dr. Sung YH for their critical review of the manuscript.

References

[1] Bower JH, Maraganore DM, McDonnell SK, Rocca WA. Incidence and distribution of parkinsonism in Olmsted County, Minnesota, 1976–1990. Neurology 1999;52:1214–20.
[2] Benito-Leon J, Bermejo-Pareja F, Morales-Gonzalez JM, Porta-Etessam J, Trincado R, Vega S, et al. Incidence of Parkinson disease and parkinsonism in three elderly populations of central Spain. Neurology 2004;62:734–41.
[3] de Lau LM, Giesbergen PC, de Rijk MC, Hofman A, Koudstaal PJ, Breteler MM. Incidence of parkinsonism and Parkinson disease in a general population: the Rotterdam Study. Neurology 2004;63:1240–4.
[4] Barbosa MT, Caramelli P, Maia DP, Cunningham MC, Guerra HL, Lima-Costa MF, et al. Parkinsonism and Parkinson's disease in the elderly: a community-based survey in Brazil (the Bambui study). Mov Disord 2006;21:800–8.
[5] Kuzuhara S. Drug-induced parkinsonism. Nippon Rinsho 1997;55:112–7.
[6] Negrotti A, Calzetti S. A long-term follow-up study of cinnarizine- and flunarizine-induced parkinsonism. Mov Disord 1997;12:107–10.
[7] Lee PH, Kim JS, Shin DH, Yoon SN, Huh K. Cardiac 123I-MIBG scintigraphy in patients with drug induced parkinsonism. J Neurol Neurosurg Psychiatry 2006;77:372–4.
[8] Rochon PA, Stukel TA, Sykora K, Gill S, Garfinkel S, Anderson GM, et al. Atypical antipsychotics and parkinsonism. Arch Intern Med 2005;165:1882–8.
[9] Tolosa E, Coelho M, Gallardo M. DAT imaging in drug-induced and psychogenic parkinsonism. Mov Disord 2003;18(Suppl 7):S28–33.
[10] Van Gerpen JA. Drug-induced parkinsonism. Neurologist 2002;8:363–70.
[11] Sethi KD, Patel B, Meador KJ. Metoclopramide-induced parkinsonism. South Med J 1989;82:1581–2.
[12] Pasricha PJ, Pehlivanov N, Sugumar A, Jankovic J. Drug insight: from disturbed motility to disordered movement—a review of the clinical benefits and

medicolegal risks of metoclopramide. Nat Clin Pract Gastroenterol Hepatol 2006;3:138–48.
[13] Chabolla DR, Maraganore DM, Ahlskog JE, O Brien PC, Rocca WA. Drug-induced parkinsonism as a risk factor for Parkinson's disease: a historical cohort study in Olmsted County, Minnesota. Mayo Clin Proc 1998;73:724–7.
[14] Negrotti A, Calzetti S, Sasso E. Calcium-entry blockers-induced parkinsonism: possible role of inherited susceptibility. Neurotoxicology 1992;13:261–4.
[15] Fahn S, Przedborski S. Parkinsonism. In: Rowland LP, editor. Merrits Neurology. Philadelphia: Lippincott Williams and Wilkins; 2000. p. 679–93.
[16] Molho ES, Factor SA. Secondary causes of parkinsonism. In: Adler CH, Ahlskog JE, editors. Parkinsons Disease and Movement Disorders: Diagnosis and Treatment Guidelines for the Practicing Physician. Totowa, NJ: Humana Press; 2000. p. 211–4.
[17] Dean CE, Kuskowski MA, Caligiuri MP. Predictors of neuroleptic-induced dyskinesia and parkinsonism: the influence of measurement methods and definitions. J Clin Psychopharmacol 2006;26:560–5.
[18] Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181–4.
[19] Lee BC, Hwang SH, Jung S, Yu KH, Lee JH, Cho SJ, et al. The Hallym Stroke Registry: a web-based stroke data bank with an analysis of 1654 consecutive patients with acute stroke. Eur Neurol 2005;54:81–7.
[20] Adams Jr HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35–41.
[21] Hu G, Jousilahti P, Bidel S, Antikainen R, Tuomilehto J. Type 2 diabetes and the risk of Parkinson's disease. Diabetes Care 2007;30:842–7.
[22] Lee PH, Yeo SH, Yong SW, Kim YJ. Odour identification test and its relation to cardiac 123I-metaiodobenzylguanidine in patients with drug induced parkinsonism. J Neurol Neurosurg Psychiatry 2007;78:1250–2.
[23] Zhang ZX, Roman GC, Hong Z, Wu CB, Qu QM, Huang JB, et al. Parkinson's disease in China: prevalence in Beijing, Xian, and Shanghai. Lancet 2005;365:595–7.
[24] Marras C, Tanner CM. Epidemiology of Parkinson's disease. In: Watts RL, Koller WC, editors. Movement disorders: neurologic principles and practice. 2nd edn. New York: McGraw-Hill medical publishing; 2004. p. 177–96.
[25] Kimura H, Kurimura M, Wada M, Kawanami T, Kurita K, Suzuki Y, et al. Female preponderance of Parkinson's disease in Japan. Neuroepidemiology 2002;21:292–6.
[26] Kim JS, Sohn YH. Current status of Parkinson's disease treatment in Korea. Parkinsonism Relat Disord 2003;9(Suppl 2):S99–104.
[27] Kim SM, Lee JS, Lee J, Na JK, Han JH, Yoon DK, et al. Prevalence of diabetes and impaired fasting glucose in Korea: Korean National Health and Nutrition Survey 2001. Diabetes Care 2006;29:226–31.
[28] Powers KM, Smith-Weller T, Franklin GM, Longstreth Jr WT, Swanson PD, Checkoway H. Diabetes, smoking, and other medical conditions in relation to Parkinson's disease risk. Parkinsonism Relat Disord 2006;12:185–9.
[29] Scigliano G, Musicco M, Soliveri P, Piccolo I, Ronchetti G, Girotti F. Reduced risk factors for vascular disorders in Parkinson disease patients: a case–control study. Stroke 2006;37:1184–8.
[30] Simon KC, Chen H, Schwarzschild M, Ascherio A. Hypertension, hypercholesterolemia, diabetes, and risk of Parkinson disease. Neurology 2007;69:1688–95.
[31] Becker C, Brobert GP, Johansson S, Jick SS, Meier CR. Diabetes in patients with idiopathic Parkinson's disease. Diabetes Care 2008;31:1808–12.
[32] Driver JA, Smith A, Buring JE, Gaziano JM, Kurth T, Logroscino G. Prospective cohort study of type 2 diabetes and the risk of Parkinson's disease. Diabetes Care 2008;31:2003–5.
[33] Sandyk R. The relationship between diabetes mellitus and Parkinson's disease. Int J Neurosci 1993;69:125–30.
[34] Pressley JC, Louis ED, Tang MX, Cote L, Cohen PD, Glied S, et al. The impact of comorbid disease and injuries on resource use and expenditures in parkinsonism. Neurology 2003;60:87–93.
[35] Lee BC, Roh JK. International experience in stroke registries: Korean Stroke Registry. Am J Prev Med 2006;31:S243–245.
[36] Woerner MG, Saltz BL, Kane JM, Lieberman JA, Alvir JM. Diabetes and development of tardive dyskinesia. Am J Psychiatry 1993;150:966–8.
[37] Postuma RB, Lang AE. Hemiballism: revisiting a classic disorder. Lancet Neurol 2003;2:661–8.
[38] Shimizu H, Shimomura Y, Takahashi M, Kobayashi I, Kobayashi S. Dopamine receptor in the streptozotocin-induced diabetic rats. Exp Clin Endocrinol 1990;95:263–6.
[39] Sernyak MJ, Leslie DL, Alarcon RD, Losonczy MR, Rosenkeck R. Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia. Am J Psychiatry 2002;159:561–6.
[40] Toprak O, Cirit M, Ersoy R, Uzüm A, Ozümer O, Cobanoğlu A, Tanrisev M, Güleç D, Cetinkalp S. New-onset type II diabetes mellitus, hyperosmolar non-ketotic coma, rhabodomyolysis and acute renal failure in a patient treated with sulpiride. Nephrol Dial Transplant 2005;20:662–3.
[41] Tonini M, Cipollina L, Poluzzi E, Crema F, Corazza GR, De Ponti F. Review article: clinical implications of enteric and central D2 receptor blockade by antidopaminergic gastrointestinal prokinetics. Aliment Pharmacol Ther 2004;19:379–80.
[42] Camilleri M. Clinical practice. Diabetic gastroparesis. N Engl J Med 2007;356: 820–9.